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NEPHROLOGY FORUM

Adequacy of dialysis revisited

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CASE PRESENTATION

Patient 1

A 50-year-old man developed end-stage renal disease (ESRD) secondary to IgA nephropathy. A teacher, he is married with teenage children and generally leads a busy life. He attended patient education classes on the options for patients with ESRD and chose automated peritoneal dialysis (APD) on the basis that it would be the least disruptive of his domestic and professional life. He weighed 80 kg. The initial APD prescription was five 2 L dwells nightly with a 2 L daytime dwell.

A peritoneal equilibration test at 6 weeks showed that he was a "low-average" transporter. Shortly afterwards, the first clearance measurements were made: the Kt/V was 2.1/week (peritoneal Kt/V, 1.5; renal Kt/V, 0.6). Weekly creatinine clearance (CrCl) was 65 L/week (peritoneal CrCl, 40 L/week; renal Kt/V, 25 L/week). He did well on APD and continued to work full-time. However, after 6 months his urine output decreased. Repeat clearance measurements disclosed a weekly Kt/V of 1.9 (peritoneal Kt/V, 1.5; renal Kt/V, 0.4), and a weekly CrCl of 55 L/week (peritoneal CrCl, 40 L/week; renal CrCl, 15 L/week). A daytime exchange was added at 5:00 each evening after the patient returned home from work. The Kt/V rose to 2.1/week and the CrCl to 61 L/week. The patient continued to do well with no peritonitis or exit-site infection episodes. The serum albumin was 3.5 g/dL and his nutrition was well maintained. His weight increased to 85 kg.

Twelve months later, the patient became anuric. His Kt/V fell to 1.7/week and the CrCl to 47 L/week. The Dialysis Outcomes Quality Initiative (DOQI) targets for APD are a Kt/V of 2.1/week and a CrCl of 63 L/week. Accordingly, his physician altered the prescription. Dwell volumes, both at night and in the daytime, were increased from 2.0 L to 2.5 L. The patient complained of daytime discomfort, however, and the daytime dwells were reduced to 2.2 L each. The Kt/V remained at only 1.9/week while the CrCl was 51 L/week. The physician, again concerned about failure to reach target levels, prescribed a second daytime exchange to be done at mid-day during the patient's lunchtime break. The patient attempted this for a while and clearance improved, but he then complained that his prescription had become too onerous. He requested that he be switched from APD to hemodialysis therapy.

Patient 2

A 57-year-old man developed ESRD secondary to diabetic nephropathy. Married with adult children, he worked as a sales clerk in a department store. One year prior to initiation of dialysis, he had chosen hemodialysis on the basis that it would be more convenient for his lifestyle. A fistula had been successfully constructed and had matured well at the time of initiation of dialysis. He weighed 68 kg.

He began a hemodialysis regimen of 4 hours three times weekly. A large-surface-area, high-flux hemodialyzer was used. His fistula had developed well and he quickly achieved a dialyzer blood flow in excess of 400 mL/min. Dialysate flow was set at 500 mL/min. The patient did reasonably well with interdialytic weight gains of 2 kg during the week and 3 kg on weekends. Serum calcium and phosphate levels generally were well controlled. Clearance measurements after 1 month showed that the Kt/V was 1.5 per treatment and the urea reduction ratio (URR) was 0.72.

The patient was aware that the DOQI target Kt/V for three times weekly hemodialysis is 1.2 per treatment and that the target URR is 0.65. He said that he did not wish to spend any more time on hemodialysis than was absolutely necessary, and he therefore requested a reduction in his dialysis time. His physician expressed concern and argued that more dialysis would lead to better outcomes for the patient. The patient insisted, however, and with each subsequent treatment, he "signed off" after 3.5 hours. A repeated Kt/V 1 month later was 1.25 per treatment and the URR was 0.67.

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DISCUSSION

Dr. Peter G. Blake (*Chief of Nephrology, London Health Sciences Centre; Professor of Medicine, University of Western Ontario, London, Ontario, Canada*): Variants of these two clinical scenarios arise frequently in the practice of both hemodialysis (HD) and peritoneal dialysis (PD). In each case, the physician acts to increase dialytic clearances in the intuitive and deeply held belief that more dialysis leads to longer survival and generally improved clinical outcomes. However, in each scenario, the patient perceives that quality of life is impaired by the dialysis regimen required to deliver the higher clearances. The question that therefore arises is whether the evidence supporting a beneficial effect of higher clearances is sufficient to justify the more onerous dialysis prescription that might be involved.

I will argue here that the medical evidence supporting the delivery of higher clearances in both HD and PD has been much weaker than is generally appreciated. Despite this, a plethora of clinical practice guidelines have advocated particular clearance targets, and the nephrology community widely believes that these targets are justified and, if anything, should be set at an even higher level [1–4]. However, two recent randomized control trials have upset conventional thinking in this area and have raised important questions about the contemporary practice of dialysis.

Hemodialysis (HD)

The roots of the dialysis community's belief in the importance of small solute clearance as a critical predictor of patient outcome lie in the National Cooperative Dialysis Study (NCDS), carried out between 1978 and 1980, and published in 1981 [5]. It is helpful for us to review this seminal study from a contemporary perspective. The NCDS involved 151 patients from eight centers who were randomized in 2×2 fashion to one of four groups. The study looked at the influence of both dialysis and blood urea nitrogen (BUN) concentration on patient outcome. Group 1 was dialyzed for 4.0 to 4.5 hours per treatment to achieve a time-averaged BUN of 50 mg/dL (18 mmol/L). Group 2 also was dialyzed for 4.0 to 4.5 hours but to a time-averaged BUN of 100 mg/dL (36 mmol/L). Groups 3 and 4 were dialyzed for 3.0 to 3.5 hours each to achieve a time-averaged BUN concentration of 50 mg/dL (18 mmol/L) and of 100 mg/dL (36 mmol/L), respectively (Table 1). To achieve the desired BUN levels, the dialyzer size, blood flows, dialysate flow rates, and direction were manipulated.

The primary end point of the NCDS study was withdrawal due to death or for medical reasons, either related or unrelated to uremia. An additional primary end point was time to first hospitalization. This study excluded patients over 70 years old and also those with diabetes and other systemic diseases, including "unstable" coronary artery disease. Therefore, the majority of a contemporary HD population would not have been eligible for this study. Patients were to receive the experimental protocol for a minimum of 24 weeks and for as long as 48 weeks if possible. Follow-up was for as long as 3 years. Interim analysis at 22 weeks showed a significantly higher morbidity rate in the two high BUN groups. Consequently, the investigators discontinued these groups prematurely. No significant difference in mortality rates was noted, but medical withdrawal rates were greater in these groups—45% and 62%, respectively—compared to 18% and 6%, respectively, in the two low BUN groups. No effect of time on medical withdrawal rates was seen. The proportion of patients hospitalized at 1 year was also significantly higher in the high BUN groups. With regard to this end point, the study discerned a trend toward an association between shorter dialysis time and more hospitalization, with a P value of 0.06. In accordance with convention, however, this trend was not reported as being statistically significant [5]. It was of note that, although the high BUN groups terminated the study early, these patients continued to do poorly even after they had resumed more standard dialysis schedules. At a subsequent analysis one year later, a higher mortality risk was noted in the patients randomized to the high BUN groups, with the risk approaching statistical significance (relative risk 2.66, $P = 0.10$).

What is not widely recognized, however, is the dose of HD that the NCDS patients were receiving when measured by today's yardsticks—the Kt/V and the urea reduction ratio (URR) [5]. As Table 1 shows, the two low BUN groups received, on average, a Kt/V of 0.85 per treatment corresponding to a URR of 0.57. The two high BUN groups received, on average, a Kt/V of only 0.45 per treatment with a URR of 0.30. The latter dose, in particular, represents a level of HD that would never be administered in normal clinical practice, either then or now. It thus might be suggested that the NCDS study was bound to have a positive result. Given that the low clearance groups received so little dialysis, it was hardly surprising that their outcomes were so poor. I do not mean to be unduly critical of this innovative and influential study, but it would be fair to say that it was not a very exacting test of the importance of dialysis dose within the current, normally prescribed clinical range.

Notwithstanding this criticism, the NCDS firmly established urea kinetics as the best measure of dialysis dose. It did not directly test clearance as a predictor of outcome, but the subsequent retrospective analysis of the NCDS data base by Gotch and Sargeant [6] introduced Kt/V to nephrology and appeared to make dialysis a more scientific practice. The NCDS therefore did not actually validate Kt/V as a measure of dialysis dose. Randomization, as already pointed out, was determined

Table 1. NCDS data[a]

Group	Time *hours*	Target TAC BUN[b] *mg/dL*	Achieved TAC BUN[b] *mg/dL* (±SEM)	~URR (—)[c]	~Kt/V (—)[b]	Midweek predialysis *mg/dL* (±SEM)	Medical withdrawal rate at 1 year (%)	Non-hospitalized at 1 year (%)
I	4.29 ± 0.03	50	51.3 ± 1.1	0.57	0.85	71.2 ± 1.4	18	86
II	4.30 ± 0.03	100	87.7 ± 1.4	0.35	0.47	104.9 ± 1.7	45	46
III	3.19 ± 0.03	50	54.1 ± 1.1	0.55	0.80	73.1 ± 1.4	6	69
IV	3.14 ± 0.03	100	89.6 ± 1.2	0.30	0.45	109.1 ± 1.5	62	31

[a] Adapted from [5]. For medical withdrawal rates, $P < 0.0001$ for effect of TAC urea; $P > 0.05$ for effect of time; for hospitalization: $P < 0.0001$ for effect of TAC urea; $P = 0.06$ for effect of time

[b] To convert blood urea nitrogen (BUN) to mmol/L, divide by 2.8; Kt/V approximations assume an nPNA of 1.0 g/kg/day (which was the mean nPNA achieved in NCDS). For nPNA range of 0.6 to 1.2, the estimated Kt/V range is as follows: for groups I and III, Kt/V range is 0.4 to 1.05; for groups II and IV, Kt/V range is 0.2 to 0.6

[c] URR approximations assume ultrafiltration and urea generation rate of 0

by BUN level and not by clearance. It is ironic that judging the adequacy of dialysis by the BUN is now considered to be a "cardinal sin," in that a low urea value fails to distinguish the well-dialyzed patient from the malnourished one. I should further point out that in the two decades since the completion of the NCDS, no randomized controlled trial has validated Kt/V as a predictor of important clinical outcomes. Multiple observational studies have shown that higher levels of Kt/V and URR are associated with improved survival but, as every student of epidemiology knows, association is not causation [7–9]. The association of high Kt/V with the good outcomes in these studies might be a confounded one. Hemodialysis units and physicians who prescribe high Kt/V might be good units or good physicians in other ways, in that they might manage other aspects or complications of the uremic syndrome well. This possibility, rather than the increased Kt/V, might explain some or all of the better outcomes. Similarly, patients who are compliant and who are willing to undergo dialysis for longer periods, or who accept and can achieve the higher blood flows, also might have baseline characteristics that contribute to their superior outcomes.

Despite this lack of high-quality proof for the validity of Kt/V as an indicator of dialysis adequacy, the nephrology community has accepted the model enthusiastically. On the basis of retrospective registry-type data, targets have been raised from the original Kt/V of 0.9 to 1.0 per treatment suggested by Gotch and Sargent to the more recent Dialysis Outcomes Quality Initiative (DOQI) target value of 1.2, which corresponds to a URR of 0.65 [2, 7]. Many have advocated raising the targets further, and the view that "more is better" is widespread. The attraction of urea kinetics to nephrologists is obvious. Here is a measure of dialysis dose (Kt/V) that is nephrology-specific, generally only understood by nephrologists, and that apparently leads to dialysis patients living longer. This measure seemingly makes the practice of dialysis more scientific. It is not surprising that many in the nephrology community adopted these notions so enthusiastically.

Against this background, the recently completed HEMO study asked whether still higher clearances would produce even better outcomes. Randomization in this important 2 × 2 study was by Kt/V as well as by dialyzer flux. In essence, the dialysis doses compared were a single-pool Kt/V of 1.6, which corresponds to a URR of 0.75, and a single-pool Kt/V of 1.2, which corresponds to a URR of 0.65 [10].

Peritoneal dialysis (PD)

Before considering the results of the HEMO study, I will turn my attention to PD, a topic admirably reviewed by Oreopoulos [11] in a previous Nephrology Forum. Once PD became established on a large scale in the 1980s, it was inevitable that the urea kinetic model would be applied to it. Teehan et al [12], in an important paper published in 1985, first measured dialytic dose in continuous ambulatory PD (CAPD) and soon Kt/V was being tested as a predictor of outcome. It quickly became apparent that the effect of clearance delivered continuously, as occurs with CAPD or with a normal kidney, was quite different from that of clearance delivered in three short but intense HD sessions weekly. It became evident that a Kt/V of 2.0 per week in PD had the same effect on BUN control as a weekly Kt/V of 3.6 delivered as three HD treatments [13]. However, controversy ensued over the explanation for this finding [13, 14].

The first outcome studies looking for associations between clearances on PD and clinical end points showed varied results [15, 16]. One of our early studies showed no adverse effect on survival for Kt/V until the level dropped below 1.5 per week [16]. Other investigators reported a more impressive effect [15]. Researchers soon recognized that much of the variation in clearances in PD was related to residual renal function, which had been reported to be better preserved on PD than on HD [16, 17]. The CANUSA study [18], published in 1996, appeared at first to establish conclusively the importance of clearances in PD. This multicenter study followed more than 600 incident CAPD patients and showed a significant association of both Kt/V and CrCl with patient

survival. Thus, for every extra 0.1 Kt/V per week, the relative risk of dying dropped by 6%. Similarly, for every extra 5 L of CrCl per week, the relative risk of dying dropped by 7%. Similar results from Maiorca et al [19] supported the CANUSA findings, and these studies were the basis of the landmark 1997 DOQI guidelines, which advocated a target Kt/V of 2.0 per week and a target CrCl of 60 L per week for CAPD [1]. Higher levels were recommended for APD on the basis that it was a more intermittent modality. However, CANUSA was a prospective cohort study and not a randomized controlled trial [20]. Just like the HD studies supporting more Kt/V, it could only show association and not causation. More important, over 90% of the CANUSA patients received the standard 4 × 2 L CAPD prescription, so changes in clearance were predominantly due to decreases in residual renal function [20]. When peritoneal clearance was analyzed separately, no independent effect was detected on survival or any other outcome [21]. Of course, it was not possible to meaningfully examine the influence of peritoneal clearance in a patient cohort in which prescriptions were so uniform [22].

In the late 1990s, a variety of data bases were examined to look at the influence of clearance on outcome in PD patients. Diaz-Buxo et al [23] and Rocco et al [24] showed the same pronounced effect that had been demonstrated in CANUSA. In each case, the effect was again totally attributable to residual renal function, and no independent effect of peritoneal clearance was apparent. The Rocco study disclosed significant variation in peritoneal clearance, which reflected the marked changes in PD prescription that were occurring in response to clinical practice guidelines by the late 1990s [24]. Despite the wide range of peritoneal clearances available for analysis, no effect of PD clearance was seen, and this led to further questioning of the importance of higher peritoneal clearance in the dose range commonly used.

Both Bhaskaran et al [25] in Toronto and Szeto et al [26] in Hong Kong tried to approach this issue by looking at anuric patients. The Toronto group retrospectively studied 122 anuric PD patients and showed an almost significant survival advantage ($P = 0.10$) in patients who had a peritoneal Kt/V greater than 1.85/week [25]. Szeto et al prospectively followed 140 anuric CAPD patients and were able to show, using multiple regression analysis, an independent effect of peritoneal clearance on mortality with relative risk reductions similar to those seen in CANUSA. However, neither of these studies was randomized, and the possibility that healthier patients were given more aggressive prescriptions with consequent confounding of results cannot be excluded.

Clearly, a prospective randomized controlled trial was required to address this issue. Early efforts had not been very successful [22]. Gotch attempted such a study in the early 1990s, but recruitment was slow and no publication resulted. Harty et al [27] completed a randomized controlled trial in 68 patients and found no outcome difference, but this study was too small and too short and thus too underpowered to detect an effect. More recently, Mak et al [28] in Hong Kong randomized 82 prevalent CAPD patients to 3 × 2 L compared to 4 × 2 L. Follow-up was for a minimum of 12 months, and no survival difference was noted between the two groups. Again, this study was significantly underpowered to detect an effect. In 1998, however, a large and well-powered, multicenter, randomized, controlled, industry-sponsored study was initiated in Mexico to address this issue. First results from the ADEMEX trial were reported in 2001 and published in 2002 [29].

Table 2. Mean values for total and peritoneal creatinine clearance (CrCl) and Kt/V in ADEMEX study[a]

	Standard CAPD	High-clearance CAPD
Peritoneal CrCl *L/week*	46	57
Peritoneal Kt/V *V/week*	1.62	2.13
Total CrCl *L/week*	53	63
Total Kt/V *per week*	1.80	2.27

CAPD is continuous ambulatory peritoneal dialysis.
[a] Adapted from [29]

The ADEMEX study. The ADEMEX study randomized 960 incident and prevalent CAPD patients at 24 centers in Mexico. A minimum of 2 years follow-up was planned. The control group received the standard 4 × 2 L daily CAPD regimen; the intervention group's prescription was altered to achieve a peritoneal CrCl of 60 L per week. This was done by increasing dwell volumes to 2.5 or 3.0 L and by adding a fifth exchange delivered via a night exchange device; APD was not used. The primary end point was patient survival, and secondary end points included technique failure, hospitalization, nutritional measurements, and infection rates. Given the nature of the intervention, it was, of course, not a blinded study. The mean age of the patients was 49 years, mean weight was 68 kg, 58% were male, and 42% were diabetic. Randomization in ADEMEX was very effective with no baseline differences between the two groups. In particular, they had similar residual renal function, body weight, co-morbidity, and peritoneal clearances at enrollment. Over the course of the study, the control group received on average a peritoneal CrCl of 46 L per week and a peritoneal Kt/V of 1.62 per week. The treatment group had values of approximately 56 L and 2.13 Kt/V per week, respectively (Table 2) [29].

The study showed no significant difference in primary or secondary outcomes between the two groups. In particular, the relative risk of death in the intervention group was 1.00. A variety of subgroups were examined, including those with and without diabetes, those with and

without residual renal function, and those above and below median body size. Again, no differences were apparent. Technique failure rates did not differ between the two groups either. Distribution of causes was not quite the same, however, with technique failure due to uremia or hyperkalemia being significantly more common in the control group. However, in interpreting this finding, one needs to recognize that this was an open-label study, and physicians might have been more likely to attribute technique failure in the control group to uremia or hyperkalemia.

A number of concerns have, nevertheless, been expressed about ADEMEX [30]. One is whether results from a Mexican PD population can be extrapolated to patients in wealthier countries. Certainly, the ADEMEX patients are younger, weigh less, and have lower serum albumin levels than do their U.S. counterparts. However, the rates of diabetes, cardiovascular morbidity and mortality, and overall survival in ADEMEX are very similar to those in western PD populations. This, as well as the consistency of the ADEMEX findings on peritoneal clearance with those from recent major North American studies, including CANUSA, greatly decreases concerns about the external validity of the study [18, 23, 24].

The question of prescription compliance in the high-clearance group also has been raised. Biochemical results from ADEMEX suggest that the bulk of extra exchanges were done and, in any case, noncompliance will always be a potential problem with the use of high clearance PD prescriptions in "real life" clinical practice.

The inclusion of prevalent, as well as incident, CAPD patients in ADEMEX has been questioned [30]. Ideally, a study should comprise incident patients only to avoid a population skewed toward those who are healthier. Conversely, however, prevalent patients are much more likely to be anuric, and it is in the anuric population particularly that one might most expect to see the benefit of high clearance PD regimens. If prevalent and predominantly anuric patients had not been well represented in the ADEMEX study, the results likely would have been criticized for just that reason. There was no beneficial trend in ADEMEX for patients either with or without urine output.

In summary, ADEMEX is a well-conducted, randomized controlled trial. It is perhaps the best study of its kind to date in the dialysis literature. It has no apparent major weaknesses. It was powered to detect a 20% reduction in the relative risk of death, and it is possible that a smaller effect might have been missed. The absence of even a minimal trend in this direction will reassure most observers that this is unlikely to be the case [29].

The HEMO study. The impact of ADEMEX on PD prescription and on nephrologists' views about adequacy of dialysis might have provided an interesting preview of the effect that the HEMO study will have on HD prescription and adequacy. This large and ambitious multicenter randomized controlled trial asked two clinically relevant questions about the relationship between HD prescription and patient outcome. Just as in ADEMEX, the answers were somewhat surprising [31].

The HEMO study was sponsored by the National Institutes of Health and carried out in 15 centers over a 6.5-year period. Patients were randomized in a 2×2 fashion on the basis of clearance and flux. The standard clearance group was targeted to achieve an equilibrated Kt/V (eKt/V) of 1.05, equivalent to a conventional single-pool Kt/V of 1.25 and a URR of 0.65. The high clearance group was targeted to achieve an eKt/V of 1.45, corresponding to a single-pool Kt/V of 1.65 and URR of 0.75. With regard to flux, the patients were randomized to low-flux dialyzers as defined by a β_2-microglobulin (β_2m) clearance less than 10 mL/min, or to high-flux dialyzers with a β_2m clearance greater than 20 mL/min. Patients had to be between 18 and 80 years of age and undergoing HD for more than 3 months. They had to be able to achieve the high clearance targets in a 4.5-hour period, so larger patients were effectively excluded. Substantial residual renal function also was an exclusion criterion, as was severe congestive heart failure or unstable angina.

The primary outcome was mortality. Secondary outcomes included hospitalization for cardiovascular disease or infectious disease, all nonaccess hospitalization, and persistent declines in serum albumin. The power calculations required 900 patients throughout the study, so the investigation had a "recruit to replace" strategy. Altogether, 1846 patients were randomized. This gave the study a greater than 80% power to detect a 25% reduction in mortality. The mean age of the enrolled patients was 58 years, mean weight was 69 kg, and 56% were female. These criteria reflected the requirement that patients be capable of achieving the high-clearance target. Almost 63% of the patients were black, 45% were diabetic, and 80% had cardiovascular disease. Patients had been on dialysis for a mean of 3.7 years prior to the study. Randomization was successful, with no baseline differences between the groups.

The patient groups were well separated over the study duration in terms of clearance and flux. The achieved single-pool Kt/Vs in the two groups were 1.32 and 1.71, corresponding to the URR values of 0.66 and 0.75, respectively. Values for eKt/V were 1.16 and 1.53 in the two groups. These differences were partly due to, on average, an extra 30 minutes of dialysis in the high Kt/V group and partly due to higher dialyzer clearance (Table 3). The study showed the expected impacts of age, race, gender, diabetes, and serum albumin level on survival. However, no difference was discerned with regard to the effects of high clearance or high flux on the primary outcome. The relative risk of mortality for the high clearance group was an insignificant 0.96 (confidence limits

Table 3. Mean values for hemodialysis (HD) prescription parameters in standard and high-clearance groups in the HEMO study[a]

	Standard clearance	High clearance
eKt/V[b]	1.16	1.53
SpKt/V	1.32	1.71
URR	.66	.75
Dialysis time *minutes*	190	219
Dialyzer blood flow *mL/min*	311	375
Dialyzer urea clearance *mL/min*	218	251

[a] Adapted from [31]
[b] Abbreviations are: eKt/V, equilibrated Kt/V; SpKt/V, single-port Kt/V; URR, urea reduction ratio

0.84 to 1.10, $P = 0.53$) and for the high flux group was 0.92 (0.81 to 1.05, $P = 0.23$).

Similarly, no differences appeared for secondary outcomes. A number of subgroup analyses, defined a priori, were performed looking at age, gender, diabetes, race, co-morbidity, years on dialysis, and serum albumin level. A significant effect of higher clearance was noted in females (but not in males) with a relative risk for mortality of 0.81 (0.67 to 0.95, $P = 0.02$). Somewhat more impressively, a significant benefit for high flux was found in patients who had undergone dialysis for more than the mean time of 3.7 years. Here, the relative risk was 0.68 (0.53 to 0.86, $P = 0.001$). The real significance of these subgroup effects is unclear, and one has to take into account that multiple such comparisons were made, leaving open the possibility that positive findings might be found by chance. The significant reduction in mortality identified for females in the high-dose group was accompanied by a trend in the opposite direction for males, with a relative risk of 1.16, although this number did not reach statistical significance. Is all this biologically plausible? Could the difference perhaps represent a weight rather than a gender effect? These questions remain to be answered. The association of high-flux HD with lower mortality in long-term HD patients is perhaps more plausible in that large-molecule toxicity might take many years to become apparent. The model for this is, of course, dialysis amyloidosis.

Although the HEMO study might have yielded disappointing results in terms of expectations in the dialysis community, it is a methodologically sound study and represents a magnificent effort on the part of the investigators, carried out over a sustained period, to address key clinical questions in the contemporary practice of HD.

ADEMEX and HEMO. What common conclusions can we draw from these two large, well-constructed, randomized, controlled trials? First, it is worth emphasizing that both these studies are major contributions to the dialysis literature. Indeed, they represent two of the three largest randomized controlled trials ever done in dialysis patients. Neither study has any apparent serious flaw. In each case, the design was good and the question asked highly relevant to contemporary clinical practice. Both have sufficient statistical power to detect a mortality reduction in the range of 20% to 25%. Neither can exclude completely a smaller reduction. However, the absence of even a hint of such a trend in ADEMEX makes it unlikely that any clinically important effect was missed by that study. In the HEMO study, the relative risk in the high clearance group tended to be below 1.0 for the primary outcome and also for most of the secondary ones. But the study never came close to achieving statistical significance, and it would be presumptuous of us to overinterpret these findings. One might speculate, however, that the appearance in the same year of these two relatively similar studies, one for each modality, will be viewed in the future as a turning point in our understanding of the adequacy of dialysis.

Is dialysis dose still important?

Before addressing further the relationship between dialysis dose and outcome, I would like to comment on residual renal function. This was an issue only in the ADEMEX study. In the HEMO study, patients were excluded if the residual renal urea clearance exceeded a very modest 1.5 mL/min [31]. In ADEMEX, however, almost one-half the patients had significant residual function and, just as was shown by the CANUSA study and other publications, a strong and apparently linear association existed between residual function and patient survival [18, 29]. This relationship between residual clearance and outcome has been less well examined in HD, but it is plausible, and indeed likely, that it is present for that modality also [32].

In contrast to this clear-cut relationship, the dose-response curve for dialytic clearance is far from clear for either modality. Obviously, zero dialysis is associated with uniformly poor outcomes, and even a modest amount prolongs life. However, ADEMEX and HEMO suggest that in the range of common clinical practice, the relationship between clearance and outcome has become "flat." From the NCDS, we know that in three-times-weekly HD, a single-pool Kt/V of 0.85 is superior to one of 0.45 per treatment [5, 7]. Somewhere between 0.85 and the 1.32 given to the HEMO control group, the dose-response curve begins to flatten out. Registry data have suggested that this flattening occurs at a Kt/V of approximately 1.2 [7, 8], although some recent studies suggest that it might occur at a higher level [33]. Registry data are full of potential confounders, however, and do not provide the strength of evidence that a randomized controlled trial does. Notwithstanding this, a reasonable assumption is that the dose of dialysis delivered to the control group in the HEMO study is at, or safely above, the theoretical point where the curve flattens out. As

such, the present DOQI guidelines for HD appear appropriate [2].

For PD, the issue is more problematic. Registry-type data bases are relatively smaller for this modality but consistently do not show any association between peritoneal clearance and survival [23, 24]. The levels of peritoneal clearance delivered to the control group in ADEMEX—a Kt/V of 1.64 and a CrCl of 46 L/week—did not put the patients at a disadvantage relative to the high clearance group, so it might be safe to assume that the break point is at or below these levels [29]. A recent, as-yet-unpublished randomized controlled trial from Hong Kong suggests that patients receiving a total Kt/V <1.7 per week indeed might have poorer outcomes [34]. On the basis of these findings, the peritoneal Kt/V probably should be kept at or above 1.7 and the peritoneal CrCl at or above 45 to 50 L/week. In both modalities, these targets can be achieved in most patients without excessively onerous prescriptions. We therefore should be reluctant to engage in a "how low can we go?" exercise by experimenting with still lower clearance levels. This is one of the dangers that dialysis patients could face if the results of these trials are interpreted as meaning that clearances are now unimportant.

Why are the effects of residual renal clearance so different from those of dialytic clearance? This should not surprise us so much. Residual renal function is associated with much more than small solute clearance. Relatively substantial residual renal function also gives the patient better volume control, better large-molecule clearance, and better endocrine and metabolic function. In many cases, it might simply reflect a generally healthier patient.

Is the yardstick wrong?

An alternate interpretation of these studies is that we are using the wrong yardstick to measure dialysis. Urea is not the definitive uremic toxin and might not be a good surrogate for the toxins that matter. The ADEMEX results suggest that creatinine is no better, and there is not much support from HEMO for the notion that middle molecules are crucial. Phosphate clearance has attracted attention recently. A solute that diffuses poorly across cell membranes, phosphate has no less than four phases of removal during HD. The toxicity and clearance kinetics of solutes such as phosphate, and also of putative protein-bound toxins, might be poorly reflected in the urea kinetic model and might, for example, be minimally influenced by short duration high-flux HD [35].

Salt and water might be the major uremic "toxins" that also have been neglected in the urea kinetic model. Longer duration HD would be expected to show benefit if this were the case. The absence of a dialysis dose effect in the HEMO study does not make such an effect less likely, given that the high-dose group received only, on average, 3.5 hours with each treatment compared to 3.0 hours, on average, for the low-dose group [31]. By most standards, both of these are "short-time" HD prescriptions. The findings of practitioners of longer duration or more frequent HD such as Charra et al [36] in France, Pierratos [37] in Toronto, and Lindsay et al [38] at this center are relevant in this regard. The benefits they describe in terms of volume and blood pressure control suggest that time and frequency are valid yardsticks by which to measure dialysis, and that this has not been sufficiently taken into account in the urea kinetic model.

Another possibility is that the urea kinetic model is deficient in that it inappropriately normalizes to body size. Lowrie et al [39] has long argued that urea clearance (Kt) without any normalization is a better, more linear predictor of patient survival in large HD data bases. Thus, the flattening out of the dose-response curve for single-pool Kt/V values above 1.2 seen in a number of U.S. data bases can be eliminated by substituting an uncorrected Kt for Kt/V. The HEMO study did not randomize by Kt and does not allow us to assess this issue directly. However, the high and low Kt/V groups did not differ at baseline in body weight and therefore did not likely differ in V. The Kt thus would be expected to be approximately 30% higher in the high clearance group, just as Kt/V was. The lack of an outcome difference suggests that higher Kt within this commonly prescribed dose range is not a more effective predictor than is a higher Kt/V. Only the borderline positive findings in females, who typically weigh less, raise the issue that at a higher Kt a benefit might have been apparent [31]. The HEMO investigators will no doubt look at this issue using their data base.

Why does clearance not have a greater effect?

Broadly speaking, two possible explanations account for the unimpressive effects of higher clearance in the ADEMEX and HEMO studies. One is that the differences in clearance between the groups in each study were too small, reflecting not so much the deficiencies of the studies but rather the limitation of our present paradigms for delivering dialysis. In other words, the increases in clearance that can be achieved with three times weekly HD and contemporary PD might be insufficient to alter outcome. It is certainly true that the efficiency of three-times-weekly HD does not increase in proportion to the Kt/V. Thus, the apparent 30% greater Kt/V in the high-dose group in the HEMO study translated into a difference of only about one-half as much in so-called "effective clearance." This small difference again raises the argument for more frequent and longer HD regimens. Here inefficiencies are much less, so each unit of Kt/V will achieve greater solute removal. Long nocturnal HD, in particular, has the scope to achieve markedly higher true clearances and might show a more

impressive effect on patient outcomes than the sort of high-dose HD used in the HEMO study.

The other possibility is that increases in clearance alone, no matter how large, might have limited potential for improving outcome. We know of no plausible mechanism by which tighter control of uremia would improve patient survival in ESRD. Once a modest amount of dialysis removes the risk of dying from hyperkalemia, uncontrolled acidosis, fluid overload, uremic encephalopathy, or severe malnutrition, it is not clear how more-intense dialysis might prolong life further. More residual renal function clearly does, but this likely works by many mechanisms in addition to small-solute clearance.

The reality is that cardiovascular disease is the biggest cause by far of mortality and morbidity in patients with ESRD [40]. Risk factors include hypertension, diabetes, smoking, and hyperlipidemia. High C-reactive protein levels, hyperphosphatemia, a high calcium-phosphate product, anemia, and perhaps hyperhomocysteinemia also may contribute to cardiovascular disease [41–44]. The extent to which any of these factors can be significantly modified by increasing dialytic clearance within the conventional range is debatable. Furthermore, the majority of ESRD patients already have a high load of cardiovascular morbidity when dialysis is initiated [40, 43]. It is plausible that any potential benefits of greater clearance are completely obscured by the overwhelming influence of cardiovascular disease on patient outcome. It might always have been naïve of us to believe that patients with congestive heart failure or widespread vasculopathy could have their outcomes substantially modified by increases, modest or otherwise, in dialytic clearance.

The future

A conclusion from all this information is not that monitoring and modification of dialytic doses are unnecessary; neither ADEMEX nor HEMO supports such a notion. The present DOQI hemodialysis targets need not be altered, although I would argue that we have little justification for pushing Kt/V values much above 1.3 per treatment [2]. The PD targets do need to be reduced somewhat, however [1, 3]. The existing targets often require prescriptions that unduly compromise patients' lifestyles and are not justified by the evidence. The practice of adding peritoneal and residual renal clearance together is no longer tenable. There should be targets for the former, and the latter should be treated as a precious bonus to be preserved as long as possible. The peritoneal Kt/V target should be in the range of 1.7 per week. It is doubtful whether CrCl adds anything to this.

With regard to dialysis prescribing, we are likely at the limit of our options with three times weekly HD and conventional PD. The question now is whether daily HD, either short or long, or continuous-flow PD [45] can improve outcomes above conventional paradigms. Small studies and sporadic reports suggest large improvements in blood pressure control and in quality of life with daily HD regimens [37, 38]. These promising results should be evaluated with the rigorous methodology of randomized control trials.

Research should focus on cardiovascular disease especially. Probably the predialysis period is the best time to intervene, but that is often not feasible for nephrologists. Particular attention should be given to the process of inflammation, ubiquitous in chronic renal failure and ESRD patients and largely unexplained [41]. Understanding and treating this cardiovascular risk factor more effectively are very important.

Finally, I would like to make a point about randomized controlled trials. The last decade has seen a number of these in nephrology. Many have yielded surprising results and upset existing notions of what is effective and what is not in renal failure. Normalization of hemoglobin in HD patients with cardiac disease [46], dietary protein restriction in chronic renal failure [47], and now, high clearance regimens in both PD and HD, as well as high-flux HD, are all strategies that nephrologists have broadly supported. Each has now come into question, however, after facing the rigor of a randomized controlled trial. The results of these trials often are disappointing to nephrologists and hard to accept because they upset preconceived notions about how things are. Their findings again emphasize that registry-based studies cannot allow us to infer causation and are frequently confounded. For all these reasons, randomized controlled trials are crucial. They challenge our thinking and give us the opportunity to redirect our specialty toward more promising strategies. Those who carry them out with great patience and over many years deserve our gratitude.

QUESTIONS AND ANSWERS

Dr. John T. Harrington (*Dean, Tufts University School of Medicine, Boston, Massachusetts, USA*): Peter, both your comments and Patient 1 demonstrate the critical importance of residual renal function to the well-being of PD patients. My specific question is, how often do patients leave PD because of total loss of renal function? Could you also comment on the issue of "lead time bias," that is, patients beginning dialysis 1, 2, 3, or more months before they actually need to.

Dr. Blake: Undoubtedly, the loss of residual renal function corresponds with the time—2 to 4 years after the initiation of PD—when many patients suffer technique failure. Is that cause and effect? Sometimes it is, but many times it is not. In most countries and most centers, the biggest single cause of technique failure in PD continues to be peritonitis [48]. Notwithstanding this, many patients appear to develop problems when they lose their residual renal function. Some have difficulties with volume overload and hypertension, and others appear to

be generally less well. ADEMEX suggests that these patients do not generally improve when we give them higher clearance PD regimens. Conversely, however, many patients who are anuric continue for a long time on PD. Oreopoulos' group has reported on a series of 140 such patients without renal function who were successfully maintained on PD [25]. So residual function is frequently a major contributor to good patient outcomes, but in many patients it is not indispensable.

The issue of lead time bias is also important. There is a great deal of interest recently in starting patients earlier on dialysis. We should not take it for granted that this strategy is beneficial. If you start patients a year earlier on dialysis, you have to take this into account when you compare them with patients who started at a more conventional time. A randomized trial on this subject is required. My understanding is that one is underway in Australia.

Your question also raises the issue of residual renal function with PD compared to HD. A number of studies show that residual function is better preserved in PD, and this is generally accepted [17]. Evidence also suggests, however, that in the United States, patients initiating PD have more baseline residual function than do those initiating HD. This difference might reflect the fact that PD patients are more likely to have started dialysis electively.

Dr. Dimitrios Oreopoulos (*Toronto Hospital, Toronto, Ontario, Canada*): I want to continue on the point that John raised. You said that the ADEMEX study showed that if patients receive more dialysis, they don't do better. Actually, the ADEMEX study showed that if you give more dialysis, patients don't survive longer. In my experience, when these patients become anuric, they are usually symptomatic, nauseated, vomiting, restless, more anemic, and they have higher phosphorus levels. In my experience, again, if you increase the dialysis dose in a large number of these patients, they do better. My question is, would you modify your recommendation that the Kt/V be 1.7 "as long as they are not symptomatic?" If they are symptomatic, I believe they should get more dialysis.

Dr. Blake: The ADEMEX study showed that not only do patients not live longer with high clearance regimens, but also they do not have fewer hospitalizations or better nutrition. Furthermore, I understand that there eventually might be data showing that these patients do not have any advantage in terms of quality of life. Notwithstanding this, every PD practitioner is aware of patients who become symptomatically uremic and then improve with an increase in the dialysis dose. Accordingly, I would agree that every patient has to be treated as an individual, and a trial of increasing the dialysis dose is reasonable in a given case. However, in a population study, this strategy generally does not seem to work. I would conclude, therefore, that we should not get too focused on clearance guidelines, but rather treat the patient as an individual, and I think that is what you were saying.

Dr. Oreopoulos: If I may go on to the HEMO study, the dilemma we have now with the findings of the HEMO study is that if you give more dialysis, you do not get additional benefits. Still, Lindsay and others like Charra and Pierratos show that if you give more dialysis, the patients do better [36–38]. Do you think it is time perhaps for us to forget completely about Kt/V and move toward time and frequency of dialysis? Should we establish ideal dialysis based on time and frequency, as Dr. Scribner and I recently recommended [49]?

Dr. Blake: I am aware of the recent hypothesis that you and Dr. Scribner have proposed [49]. I think there is a case to be made for your approach, but I think it is too early to dismiss Kt/V altogether. I have tried to emphasize here that there is no evidence that higher Kt/Vs are better than so-called conventional Kt/Vs, but evidence in both modalities indicates that there is a lower limit of Kt/V below which we should not let our patients fall. It is not justified to say that Kt/V should be dismissed. It would be very dangerous to our patients if we ignored the issue of clearance altogether after these two negative studies. However, I do agree that it is time to look at other yardsticks for measuring dialysis. A new hypothesis is very welcome in that regard. If a new yardstick is accepted, I think we should validate it in a clinical trial more promptly than was the case for Kt/V.

Dr. Peter Cordy (*London Health Sciences Centre, London, Canada*): I have two questions. You said that the practice of adding peritoneal and residual renal clearance together is no longer tenable. Do you mean that if a patient has a peritoneal clearance of 1.5 and a renal clearance of 0.4, you would then ensure that the peritoneal clearance be increased to greater than 1.7?

Dr. Blake: Yes, I do. In general, I think peritoneal and residual renal clearance should be regarded as two very distinct entities. ADEMEX tells us that the former cannot replace the latter, so adding them together is not really justifiable. Truly, these are the proverbial "apples and oranges." ADEMEX tells us that a peritoneal clearance of 1.64 is as good as one of 2.12, but it does not tell us that it is safe to go below 1.64. Obviously, in patients with very substantial renal function, it is possible to manage them initially on low-clearance dialysis regimens, so I might modify my opinion if the patient had a residual renal Kt/V greater than 1.0 per week. Our clinical experience tells us that such patients tend to do well.

Dr. Cordy: What you say follows from the ADEMEX study. On the other hand, we know that renal clearance is much better than peritoneal clearance, so one would have to say that someone who has a Kt/V of, for example, 1.8 from peritoneal clearance probably is not as well off as someone who is achieving some of that from residual renal function. That was really my point.

Dr. Blake: Again, I agree with you. The patient with a greater contribution from residual renal function will tend to be better. My point, however, is that you can't replace the residual function, one for one or unit for unit, with peritoneal clearance and hope to have the same beneficial effect on patient survival or other outcomes.

Dr. Cordy: You might have partially answered my other question. If more is not necessarily better, and a certain amount, for example, a Kt/V of 1.8, is sufficient, should we now revert to CAPD and "classic" CCPD as opposed to automated therapy with at least one daily exchange?

Dr. Blake: I think much of the move to APD over the past decade reflects patient choice. Physicians might have been inclined to prescribe more APD for adequacy reasons, but the patient perspective was that APD is associated with a better lifestyle. Accordingly, most patients, if given a choice, will not be willing to use standard CAPD instead of APD. However, I think standard CAPD was discarded too precipitously in many centers. It is an excellent therapy for many patients. As we know from the Canadian registry, the survival results achieved with CAPD are excellent [50].

Dr. Mukesh Khandelwal (*Bombay Hospital, Mumbai, India*): You described a patient on APD, and the ADEMEX study included patients on CAPD, so can we extrapolate these results to APD patients?

Dr. Blake: Your question concerns whether the ADEMEX results can be extrapolated to APD patients. This is a concern. The ADEMEX study comprised only CAPD patients, and the high-clearance group used night exchange devices and larger dwell volumes but did not use cyclers. Strictly speaking, the results therefore cannot be applied to APD. I would ask, however, whether APD is so very different from CAPD. I do not think that anyone is going to repeat the entire trial in APD patients. I think this is the best evidence we are going to have, and my view is that the same principles apply to both modalities. I cannot prove this, but it seems a reasonable supposition.

Dr. Rita Suri (*London Health Sciences Centre*): The practice of high-efficiency, short-time hemodialysis, widely implemented after the NCDS, appeared to dismiss the effect of dialysis time, and many physicians attributed the high mortality rates on dialysis in the 1980s in the United States to the fact that this practice was widely followed. Do you think that the HEMO study now provides renewed justification for this practice and, given what happened after the NCDS, what do you anticipate the long-term outcomes will be?

Dr. Blake: Yes, I think this is a danger. It would be a shame if the HEMO study were interpreted as meaning that low Kt/Vs and short dialysis times are safe. Some might interpret the HEMO study as indicating that dialysis times averaging 3 hours in a group of patients who weigh a mean of 68 kg are reasonable. This is a concern to a lot of nephrologists outside the United States, especially those who have long been uneasy with the short dialysis times used in some U.S. centers. Many of us wonder whether control of blood pressure and cardiovascular outcomes might have been better in the HEMO study if the patients had received 4 to 5 hours instead of 3 to 3.5 hours of treatment. I would therefore emphasize the fact that the control group in the HEMO study got a Kt/V of 1.3 per treatment and that the DOQI guidelines for HD adequacy still apply. I do not think the HEMO study allows us to draw any conclusions about the importance of dialysis time. I will continue to argue that the most important determinant of dialysis time should be the patient's need for adequate fluid removal and optimal blood pressure control.

Dr. Jatin Kothari (*King Edward Memorial Hospital, Mumbai, India*): You mentioned a minimum target for peritoneal Kt/V of 1.7. The control group in ADEMEX had a Kt/V of 1.62, and the group from Toronto showed that if a patient has a Kt/V of less than 1.8, the outcome is worse [25]. Should we have any minimum target value for the Kt/V, or should we individualize treatment for each patient? My second question is, do you think that more people should start with PD as first-line therapy, unless contraindicated, since we know it preserves residual renal function for a longer duration than does HD?

Dr. Blake: In answer to your first question, I think a peritoneal Kt/V of 1.7 is a reasonable cutoff. The Bhaskaran study suggested a value of 1.85, but it was a retrospective study with consequent potential biases, so the randomized controlled trial would take precedence [25].

I agree that more patients should use PD as an initial therapy. There is convincing evidence that it preserves residual renal function better than HD. More important, there is evidence from the United States, Canada, and elsewhere that patient survival on PD is at least as good—and perhaps better—than that on HD in the early years of dialysis [50, 51].

Dr. Louise Moist (*London Health Sciences Centre*): My first question is related to the ADEMEX study. As you pointed out, the overwhelming cause of death was from cardiovascular disease and infection. But the more concerning point for a nephrologist was that congestive heart failure was responsible for 13.4% of deaths in the control and only 5.7% in the intervention subjects. Similarly, as you pointed out, uremia, hyperkalemia, and acidosis contributed to 12.2% of deaths in the control and 5.1% in the intervention groups [29]. As nephrologists, we are in the business of dialysis, and the deaths from those causes—congestive heart failure, uremia, acidosis, and hyperkalemia—are the ones that we try to prevent from day to day. Do you think the more challenging causes of death—coronary artery disease and infection, as you mentioned—will have to be dealt with earlier,

such as in a chronic renal failure clinic, before we get to the dialysis unit? So my real question is, if we adopt a low-dose dialysis prescription, do you think we will be seeing more of the dialysis-related deaths, those that we have been trying to prevent over the last several years?

Dr. Blake: With regard to your first point, I do note the higher rates of death attributed to congestive heart failure, uremia, hyperkalemia, and acidosis in the control as compared to the intervention group in the ADEMEX study. However, there was no overall difference in death rates between the two groups, and one has to be mindful that this was an "open-label" study. I strongly suspect that the "unblinded" physicians were more likely to attribute death or technique failure to diagnoses such as uremia and congestive heart failure when they occurred in the control group. This is not, in my view, a convincing finding. We are left with the "hard" result showing no difference in survival between the two groups.

With regard to your second point, I agree that cardiovascular disease needs to be tackled earlier—in the chronic renal failure clinic or even before that. For many patients, end-stage renal failure occurs at a late phase in the progression of the cardiovascular disease that ultimately determines their life expectancy. Modification of risk factors much earlier is surely the way to go forward here.

Dr. Moist: Do you think we should have population-based dialysis dose targets as recommended by DOQI and the CSN, or should we develop individualized targets based on gender, your data, patients' lifestyles, clinical symptoms, and laboratory parameters?

Dr. Blake: In an ideal world, we might generate and individualize targets to each patient based on gender, lifestyle, life expectancy, and other factors. In practice, we need to simplify things a little, and I still think there is a role for overall dialysis-dose targets. The important point is not to see these as something rigid and immutable, but rather as one of many parameters that are part of the overall patient management plan.

Dr. Harrington: Are there long-term studies of 10- to 20-year survivors in either HD or PD? Such studies might provide clues as to how we can improve care for the rest of the population. They could also be rich sources of data for functional genomics studies.

Dr. Blake: There are some data on this in PD [52]. Long-term survivors are, of course, more likely to be patients who initiated dialysis at a younger age. Similarly, less baseline co-morbidity is associated with better survival. Other factors associated with long-term survival include female gender, Asian race, and smaller body habitus. I know of no evidence that any particular genotype predicts better survival, however.

Dr. Robert Lindsay (*London Health Sciences Centre*): The human kidney is unbelievably efficient; it works continually whether native or transplanted. This is the ideal for renal replacement therapy. Peritoneal dialysis is certainly continuous, and that might be where its benefit lies. The bad side about PD is that it is somewhat inefficient. You, Dr. Oreopoulos, and others have tried to increase efficiency, but you are limited by how much fluid you can put in per unit time, what surface area exists, and so on. All your modifications of trying to alter the membrane permeability, frankly, just did not work. So we are kind of stuck. Hemodialysis is actually extremely efficient, but the problem is its discontinuity. When you think about it, how we got into the paradigm of three-times-a-week HD and have stuck there for the last 25 or 30 years is not in any way based on human renal physiology. That regimen came as an unfortunate middle-of-the-road compromise among three factors: what little we knew about adequacy, what patients and nurses would tolerate, and the economics. Usually these three were pulling in different directions. I think the issue now is how we can change the current treatment paradigm. The beauty of HD is that we can decrease its discontinuity and make it much more like a continuous therapy, with quotidian overnight or "short-hours" daily therapy. The HEMO study tells us that there is little or nothing to be gained by increasing the efficiency of a single treatment to beyond that already established when it is used only three times per week. I do not think that is too surprising. We now have to study what happens when we increase the frequency.

Dr. Harrington: Dr. Lindsay, what is the evidence for the sermon you just gave us? Do you know that quotidian overnight dialysis works?

Dr. Lindsay: I know that it works from our own prospective, cohort-controlled study [38]. But I do agree that there has not been a randomized prospective study on survival, and that enough evidence supports conducting a randomized prospective study of quotidian HD versus conventional HD.

Dr. Mohammed Alsunaid (*King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia*): Do you think that we should disregard weekly CrCl in assessing the adequacy of dialysis, and look only for urea clearance, Kt/V?

Dr. Blake: I am very sympathetic to this point of view. I think we have made a mistake in PD by having far too many targets. Let me summarize what we have at present. We have Kt/V and CrCl targets. We have targets for CAPD and APD with and without day dwells. We also have targets for high and low transporters. So we end up with about 12 different permutations. There is simply no clinical evidence to support all this and it has made PD too complex. There is a danger of putting off all but the most enthusiastic PD practitioners. My view is that CrCl does not add anything above and beyond Kt/V. Studies that show CrCl to be a better predictor of outcome merely reflect the fact that it gives higher weight to residual renal outcome. I would advocate that we have

one peritoneal clearance target for all PD modalities, and it is probably best expressed as Kt/V.

Dr. Efstathia Tziviskou (*Red Cross Hospital, Athens, Greece*): The control group in the ADEMEX study had a very low serum albumin. It has been standard teaching that in the absence of inflammation, as evidenced by an elevated CRP, a patient with low serum albumin should have the dialysis dose increased. Actually the treated group had a serum albumin increase. Would you agree that malnourished CAPD patients, in the absence of inflammation, should have the dialysis dose increased?

Dr. Blake: There are two issues here. First, the serum albumin levels were indeed low in the ADEMEX study, and one might be inclined to think this simply represented malnutrition in patients who live in Mexico. It is not as simple as that, however. The albumin measurements in ADEMEX were done by what is called nephelometry and not by the standard bromocresol green and purple methods that most of us are familiar with. Nephelometry tends to give albumin results that are about 0.3 g/dL lower, so the serum albumin in ADEMEX can translate into something in the 3.2 to 3.3 g/dL range, with which we are more familiar.

A second issue is whether higher peritoneal clearance increases serum albumin concentration. You are correct that the serum albumin levels in the treated group were slightly higher at the end of the study than in the control group. However, they were also slightly higher at baseline, although the difference was not significant. The authors therefore looked at the change in serum albumin during the study, and this did not differ between the two groups. I would not want to overinterpret the effect of peritoneal clearance on albumin. I am not convinced that there is a real effect.

Dr. Harrington: From what I have heard today and read earlier, it seems that Kt/V is not much better than the simpler URR. Are there good studies looking at one versus the other to measure patient outcome?

Dr. Blake: No, no studies show that Kt/V is any better than URR, but the two are highly correlated. Both appear to be equally predictive of patient survival in major data bases. In theory, URR does not reflect convective clearance and does not allow the individual components of the HD prescription to be dissected out. There is, of course, a whole literature of HD based on the relative merits of the various types of Kt/V—equilibrated and standardized, double-pool and single, and so on. The reality, however, is that a unit would likely be just as effective in avoiding morbidity and mortality due to inadequate HD if it simply monitored URR and assured that every patient attained a value of 0.65 or over.

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